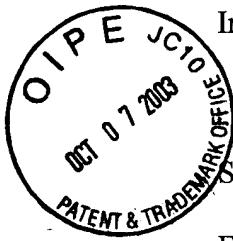


#5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re Application of: )  
DVORSKY et al. ) Art Unit: 3737  
Serial No.: 10/060,561 )  
Filed: January 30, 2002 ) Examiner: Barry Pass  
For: APPARATUSES, SYSTEMS AND )  
METHODS FOR EXTRAVASATION )  
DETECTION )

DECLARATION UNDER 37 C.F.R. § 1.131  
TO OVERCOME CITED U.S. PATENT REFERENCE

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

RECEIVED  
OCT 16 2003  
TECHNOLOGY CENTER R3700

Dear Sir:

This Declaration is being filed to establish completion of the invention of Claims 7, 11, 16, 18 and 23 in this patent application in the United States on a date before February 2, 2001, which is the earliest priority date of cited U.S. Patent Application Publication No. 2002-0172323 to Karella et al. ("the Karella patent").

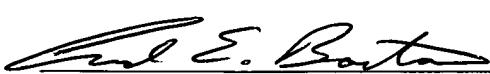
To establish the date of completion of the invention of Claims 7, 11, 16, 18 and 23 in this patent application, the following document is submitted herewith as evidence: "Extravasation Phase 2 Final Report" (including experimental set-up and results, and photographs).

From the enclosed document, it can be seen that the invention of Claims 7, 11, 16, 18 and 23 in this application was made at least by the date of June 8, 1999 (i.e., the date of the report), which is a date earlier than the earliest priority date of the Karella patent.

This Declaration is made and executed by Mr. Chad Bouton, a named inventor of this application and the author of the accompanying "Extravasation Phase 2 Final Report."

This Declaration is being submitted in response to the rejection of Claims 7, 11, 16, 18 and 23 based on the Karella patent in the Office Action mailed on June 3, 2003.

As a named inventor signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Name of Inventor: Chad E. Bouton  
Signature of Inventor:   
Date: October 1, 2003  
Citizenship: United States  
Residence: Delaware, Ohio  
Post Office Address: 312 Pecan Court  
Delaware, OH 43015

# Extravasation

## Phase 2 Final Report

### for Medrad Incorporated

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C. Bouton

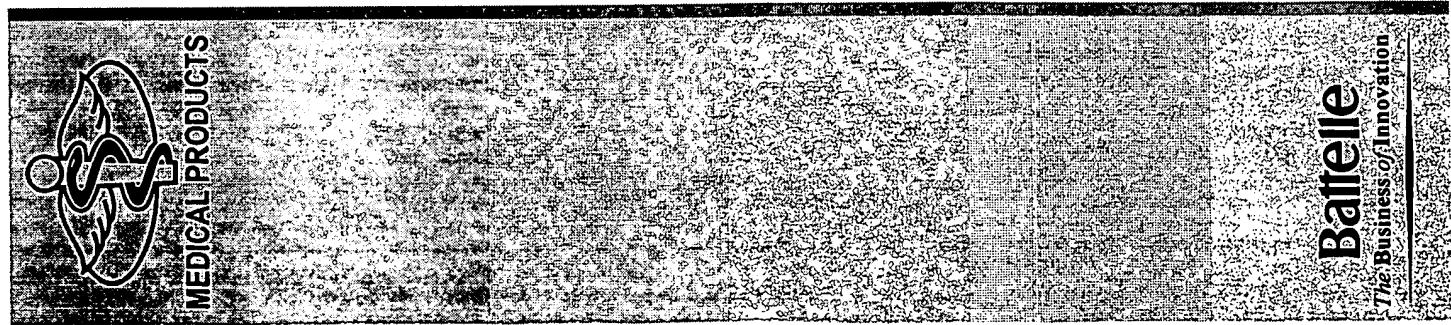
June 8th, 1999



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# Introduction and Phase Summary



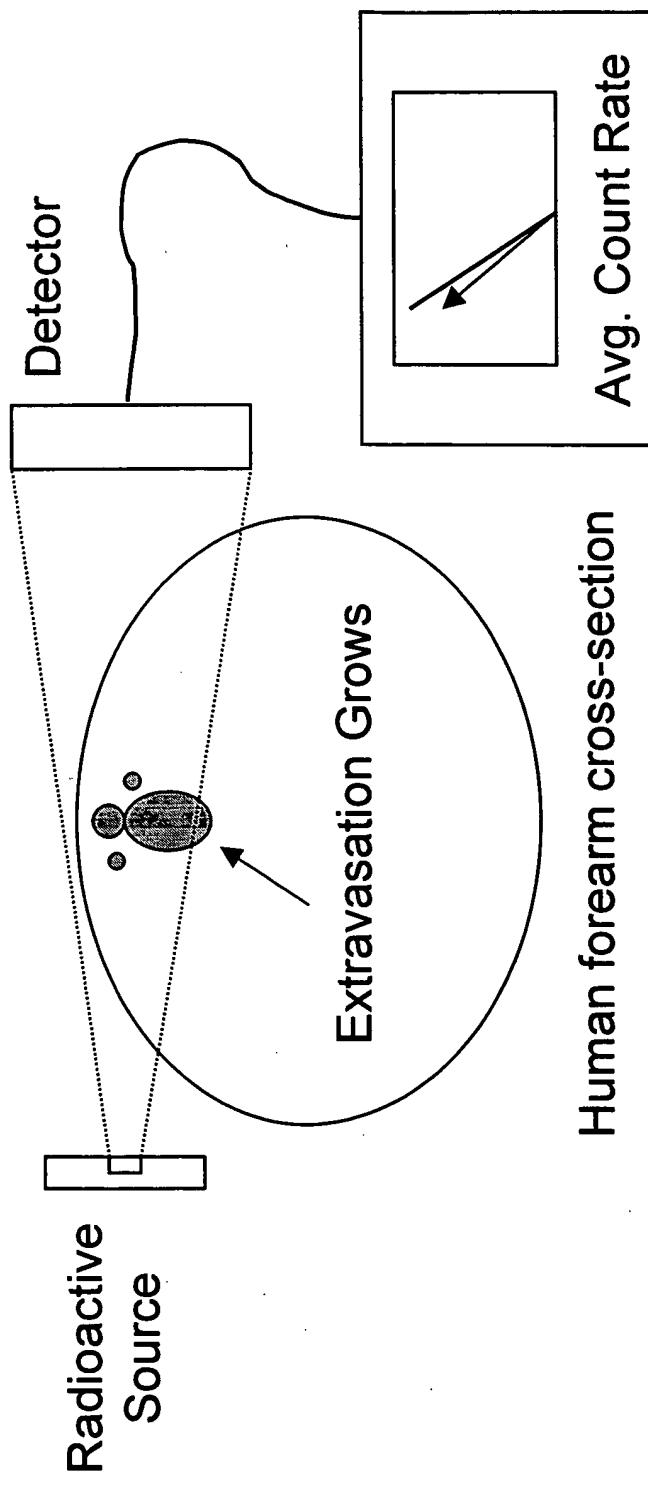
# Introduction

- Review Radioactive Source-Detector Concept
- Phase 1 key objectives
  - CM radioactive photon absorption characteristics
    - Iodine concentration
    - Shape
  - Basic response time predictions



# Introduction

- Review Radioactive Source-Detector Concept



Medrad Extravasation Phase 2, 6-8-99



# Introduction

- Review Radioactive Source-Detector Concept
- Phase 1 key objectives
  - CM radioactive photon absorption characteristics
    - Iodine concentration
    - Shape
  - Basic response time predictions



## Introduction (cont.)

- Phase 2 key objectives

- Detector efficiencies (GM and CZT)

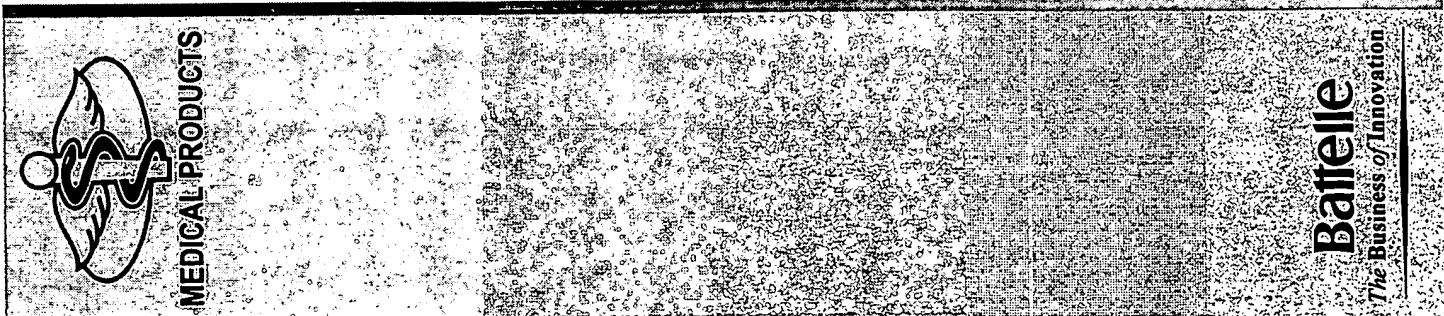
- Impacts patient dose

- Improve phantom (size, skin, add bone)

- Investigate single and complementary (dual) source-detector (S-D) pairs

- Increase sensitivity / decrease false alarms

- Dual: decrease patient arm motion sensitivity



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## Introduction (cont.)

- Phase 2 key accomplishments

- Detector efficiencies (GM, CZT, Xe, Si)
- Investigated alternative detector technologies  
Xe, Si diodes, aSe  
Scintillating fiber: Battelle-managed Pacific  
Northwest National Laboratory (PNNL)
- Improved phantom (size, skin, bone)
- Verified water absorbs and scatters radiation  
similarly to soft tissue
- Used energy spectral analysis



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Medrad Extravasation Phase 2, 6-8-99

# Introduction (cont.)

- Phase 2 key accomplishments (cont.)
  - Two new concepts for modes of detection
    - X-ray fluorescence
    - Scatter mode (backscatter allows co-located S-D)
  - Discovered using Iodine-129 as a source may be superior to using Americium-241
    - Completed simple model with energy variable
    - Discovered optimal energy range
    - Searched through Nuclide database
  - Investigated source-detector *arrays* (fundamental)
    - Increased sensitivity / decreased false alarms
    - Decreased S-D motion sensitivity
    - Enlarged search volume



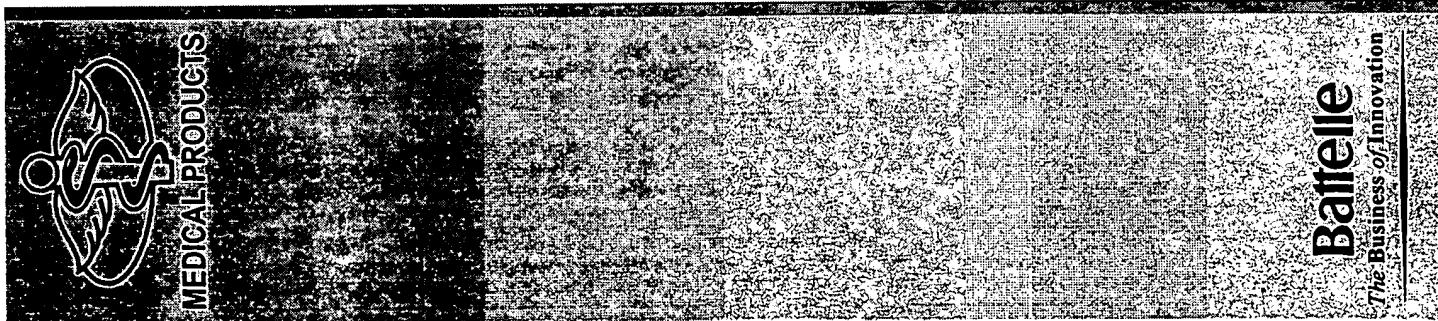
MEDICAL PRODUCTS

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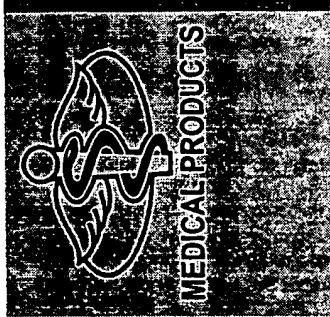
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## Introduction (cont.)

- Phase 2 key accomplishments (cont.)
  - Determined key system performance factors
  - Measured dose rate and predicted patient dose
  - Completed S-D motion experiment to determine level of importance
  - Completed initial evaluation of energy windowing effectiveness with Am-241 (should try Co-57)



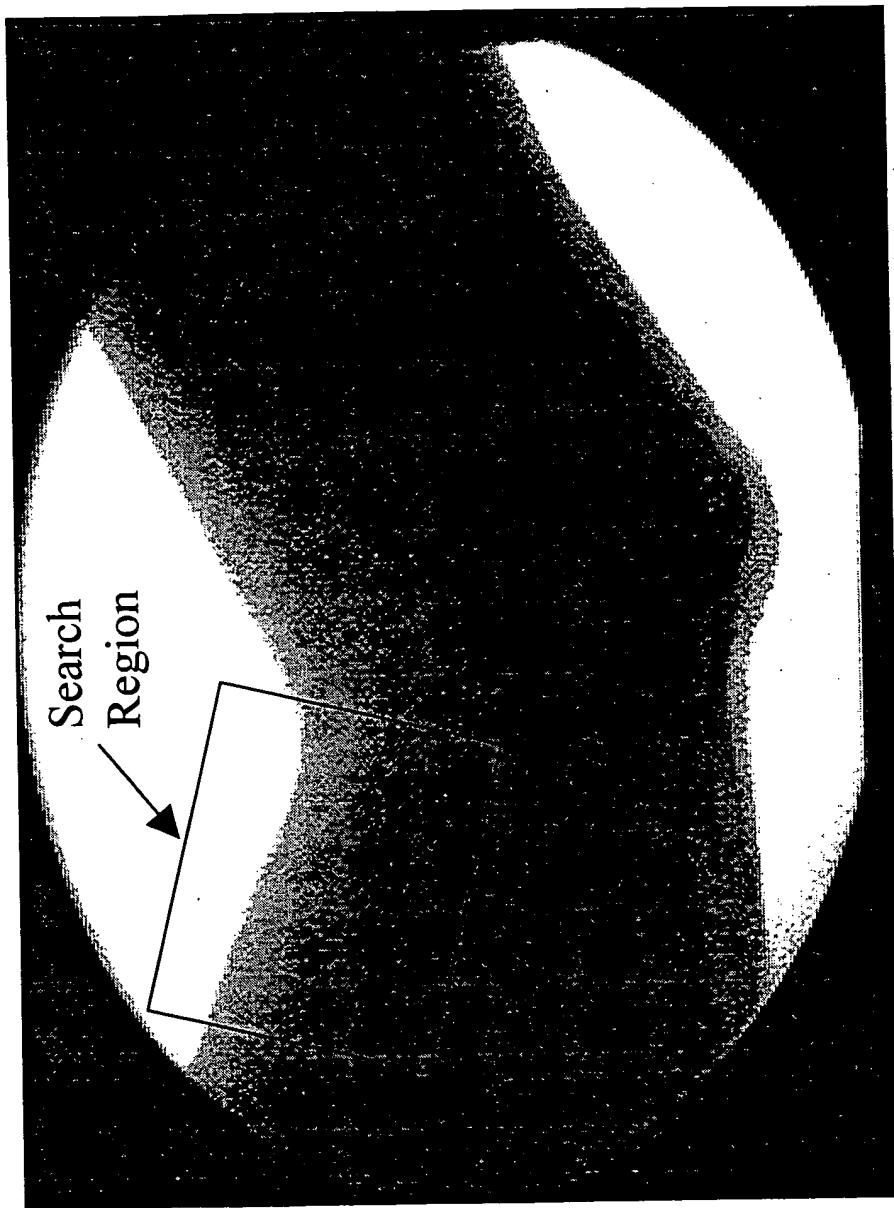
# Detector Efficiencies



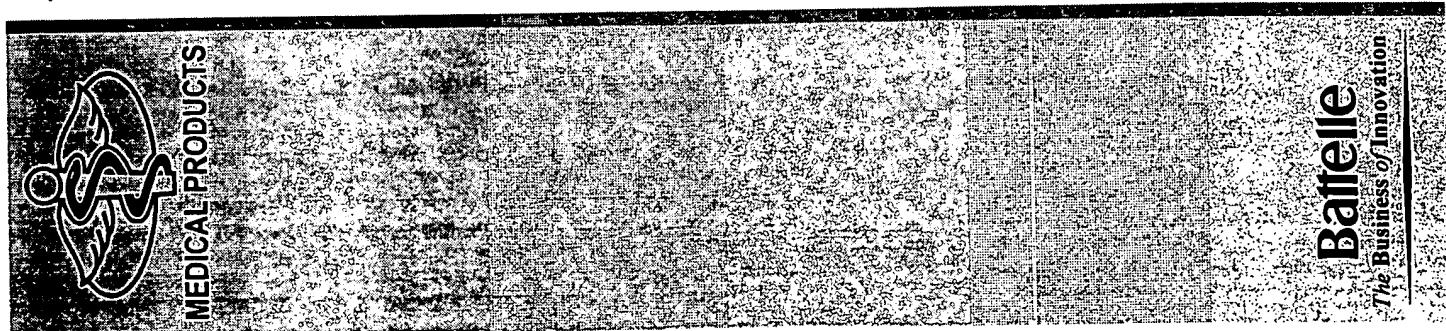
Detector Type	Manufacturer, Model	Shape, Active Area Size	Cost/Qy.	Counting Efficiency for 60 keV Gammas	Information Source
Geiger-Mueller Tube (#1)	LND, 7311	Round, 44.5 mm diam.	\$75/1	1%	Determined Experimentally at Battelle
Geiger-Mueller Tube (#2)	LND, 7311	Round, 44.5 mm diam.	\$75/1	1%	Determined Experimentally at Battelle
CZT	eV, custom	Round, 14.7 mm diam	—	95%	Determined Experimentally at Battelle
Xenon Gas Filled Proportional Counter	LND, 4312	Round, 44.5 mm diam.	\$425/1	10%	Determined by Manufacturer
Silicon (300 $\mu$ m thick)	Detection Technology, XRB 50s-CB	5x5mm	\$69.80/1 \$22.30/1000	2%	Determined by Manufacturer

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# Improving the Phantom

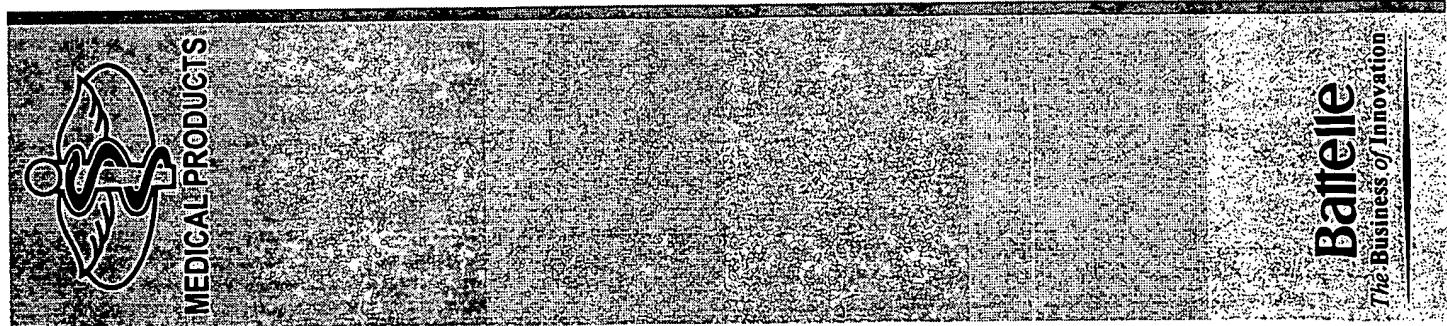
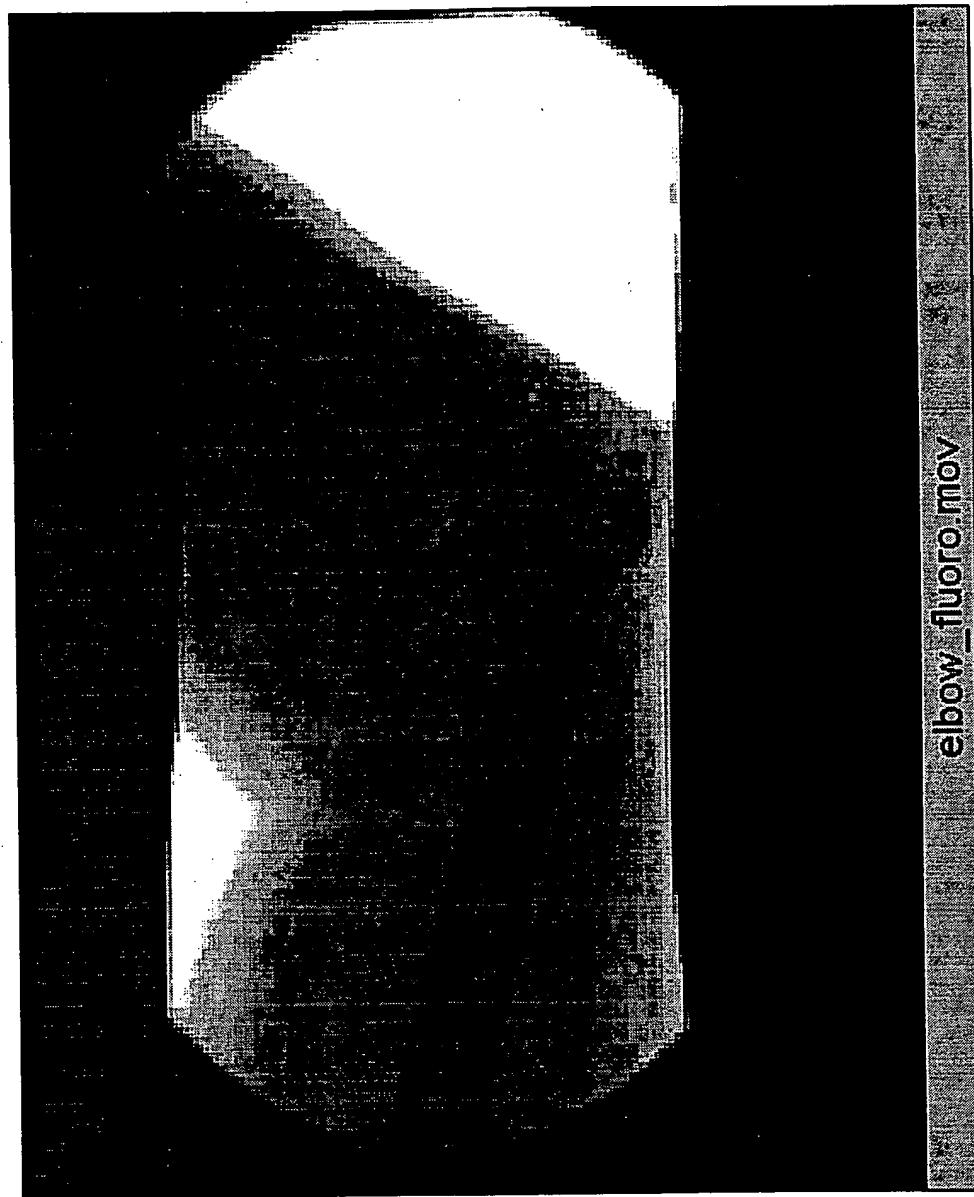


Fluoroscope Image of Human Elbow



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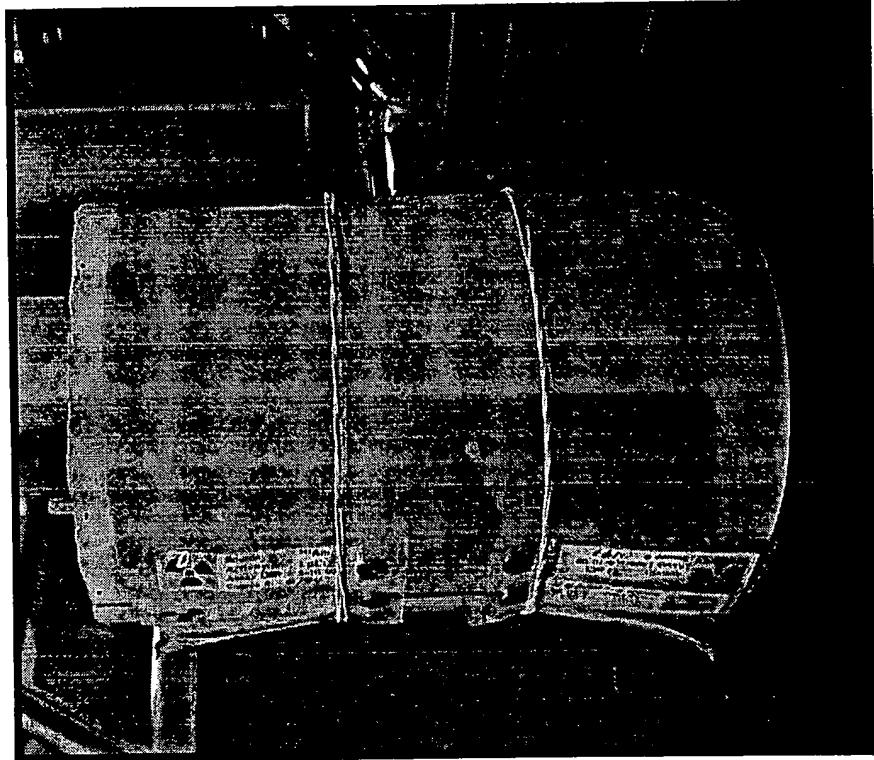
# Improving the Phantom (cont.)



Medrad Extravasation Phase 2, 6-8-99

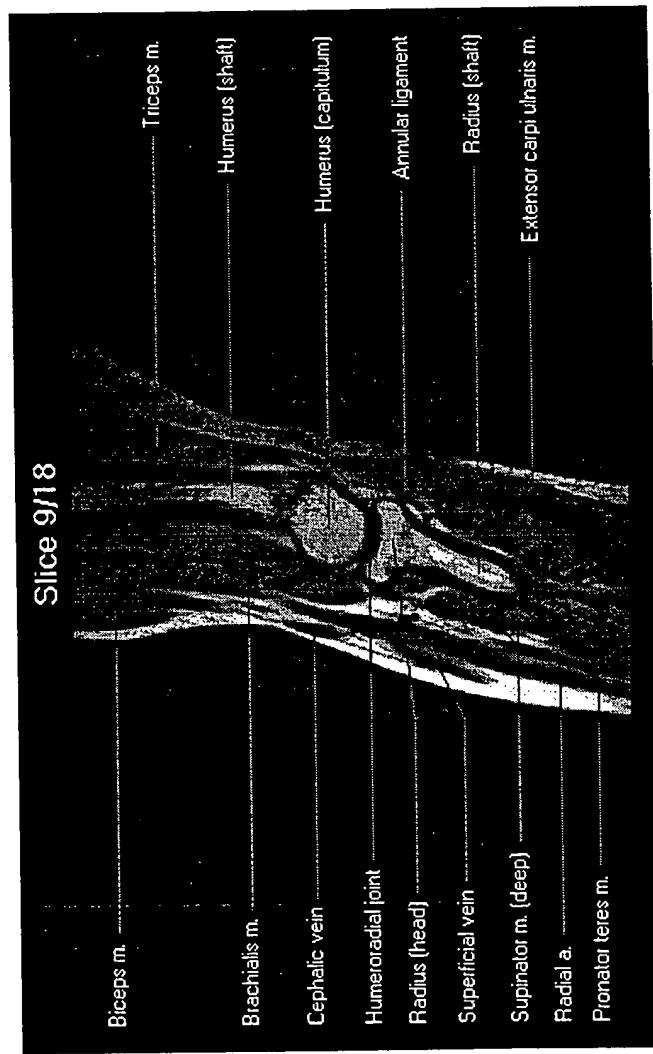
## Improving the Phantom (cont.)

- Larger (9cm diam.)
  - 75th % male elbow bend
  - >100th % female
  - >90th % total pop.
- Better skin
- Bone included
  - epoxy resin
- Balloon used

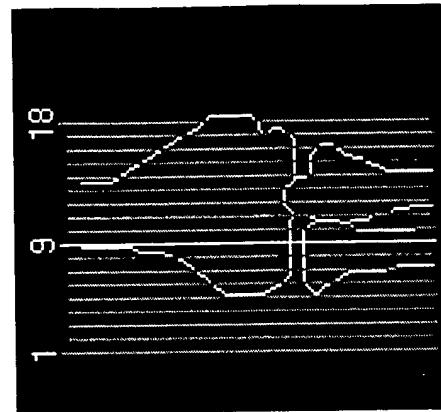


# Improving the Phantom (cont.)

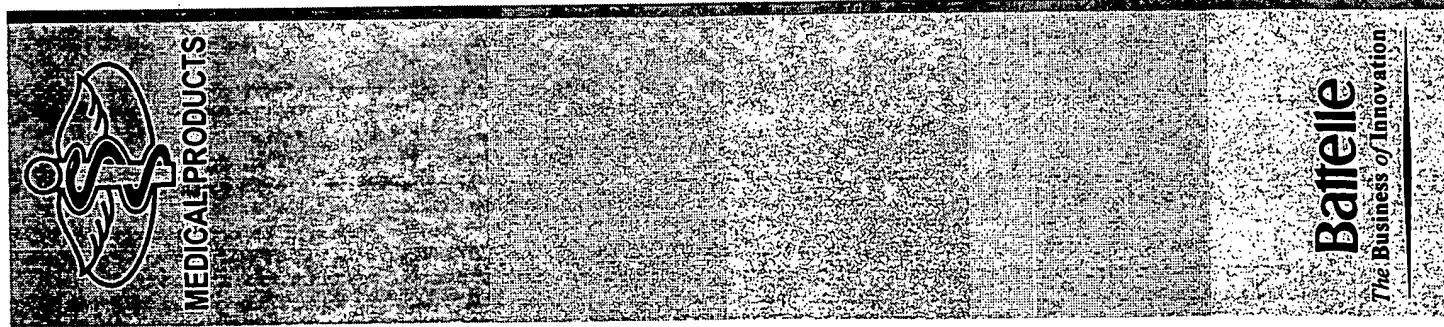
## Sagittal - Medial (Inside of Arm) View



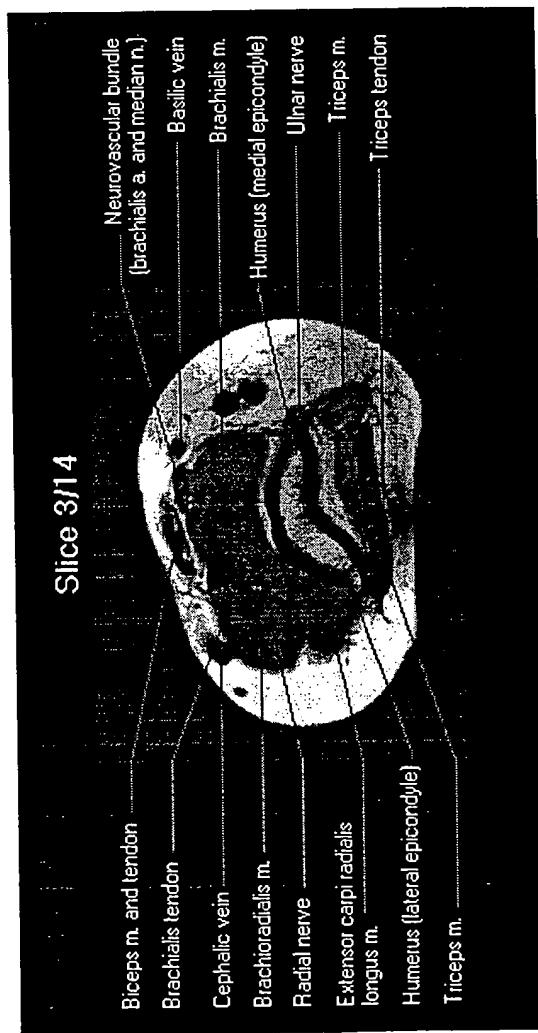
Cross-Section Location  
Anterior (Front) View



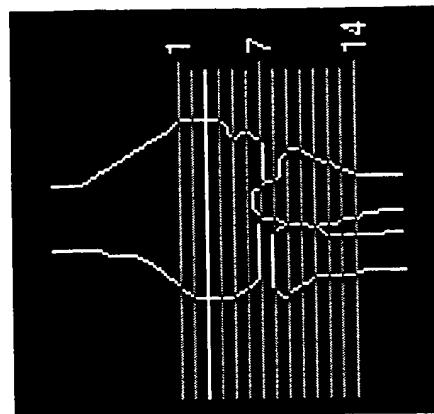
# Improving the Phantom (cont.)



Transverse - View from Distal (Hand) End

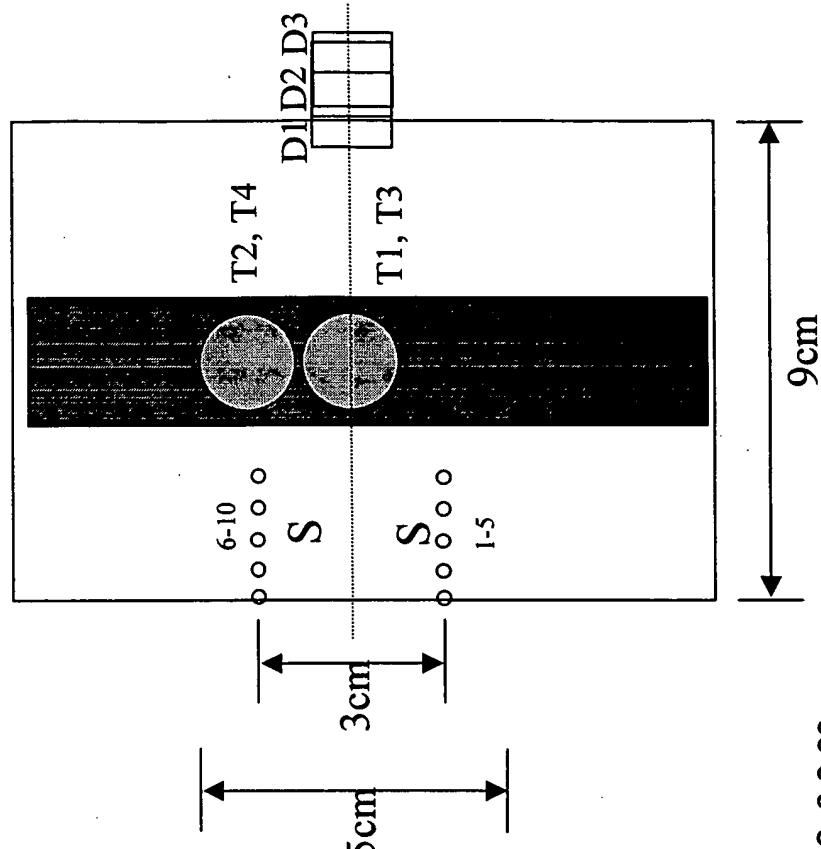
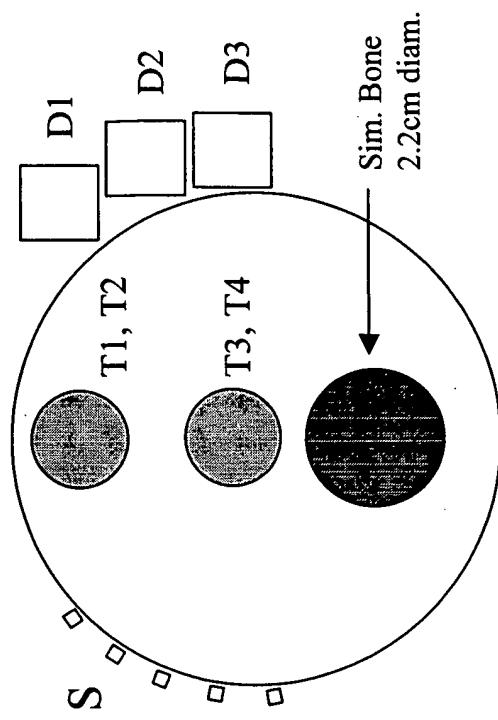


Cross-Section Location  
Anterior (Front) View

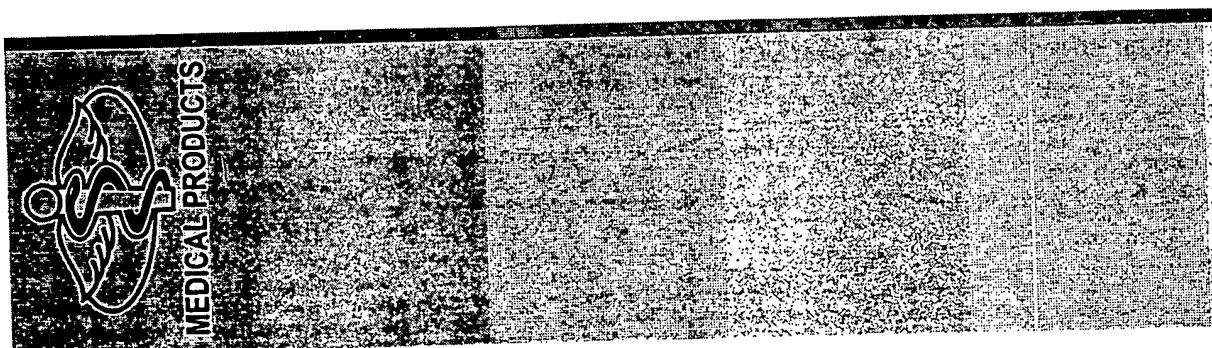
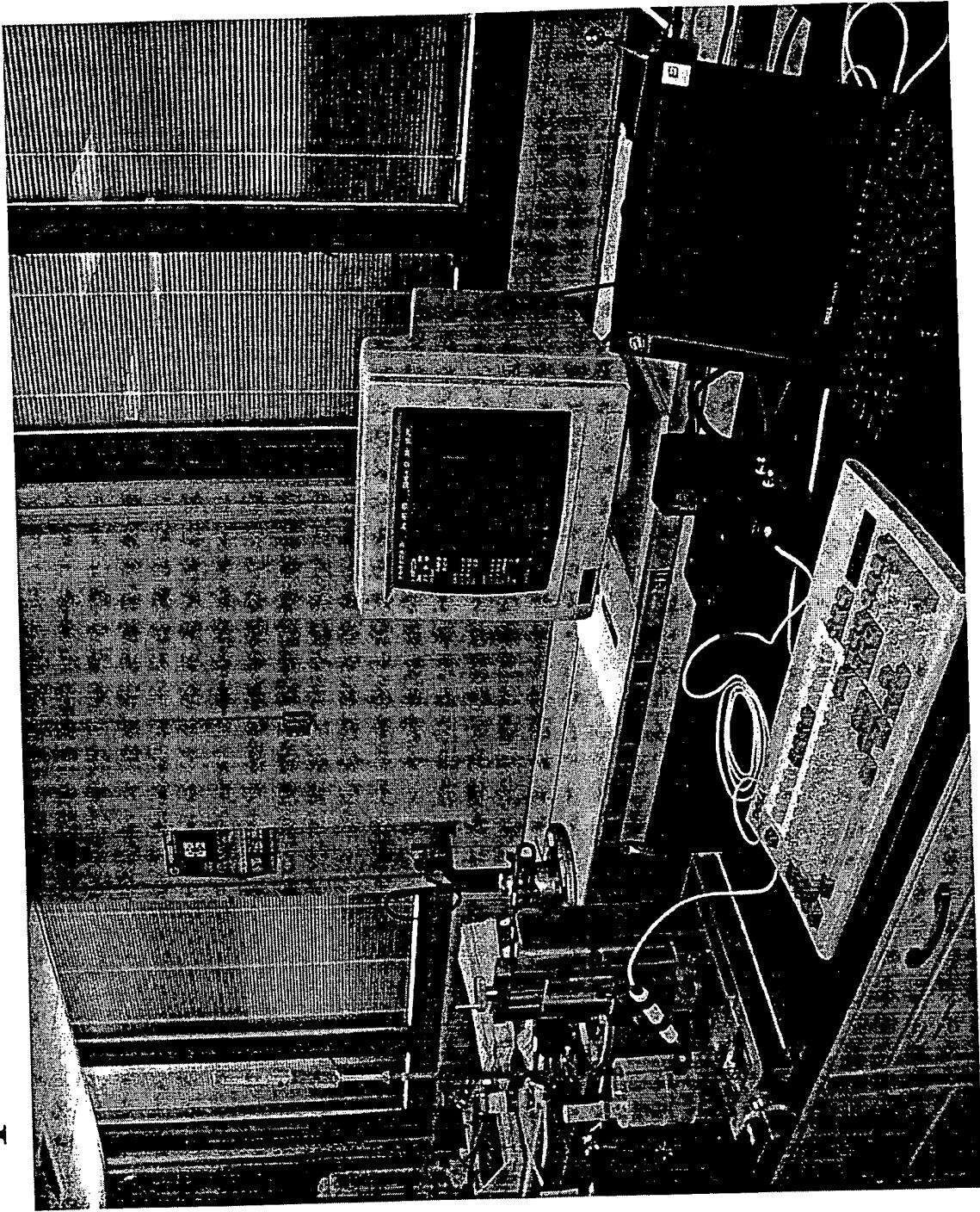


# Improving the Phantom (cont.)

S = Source  
D = Detector  
T = Target



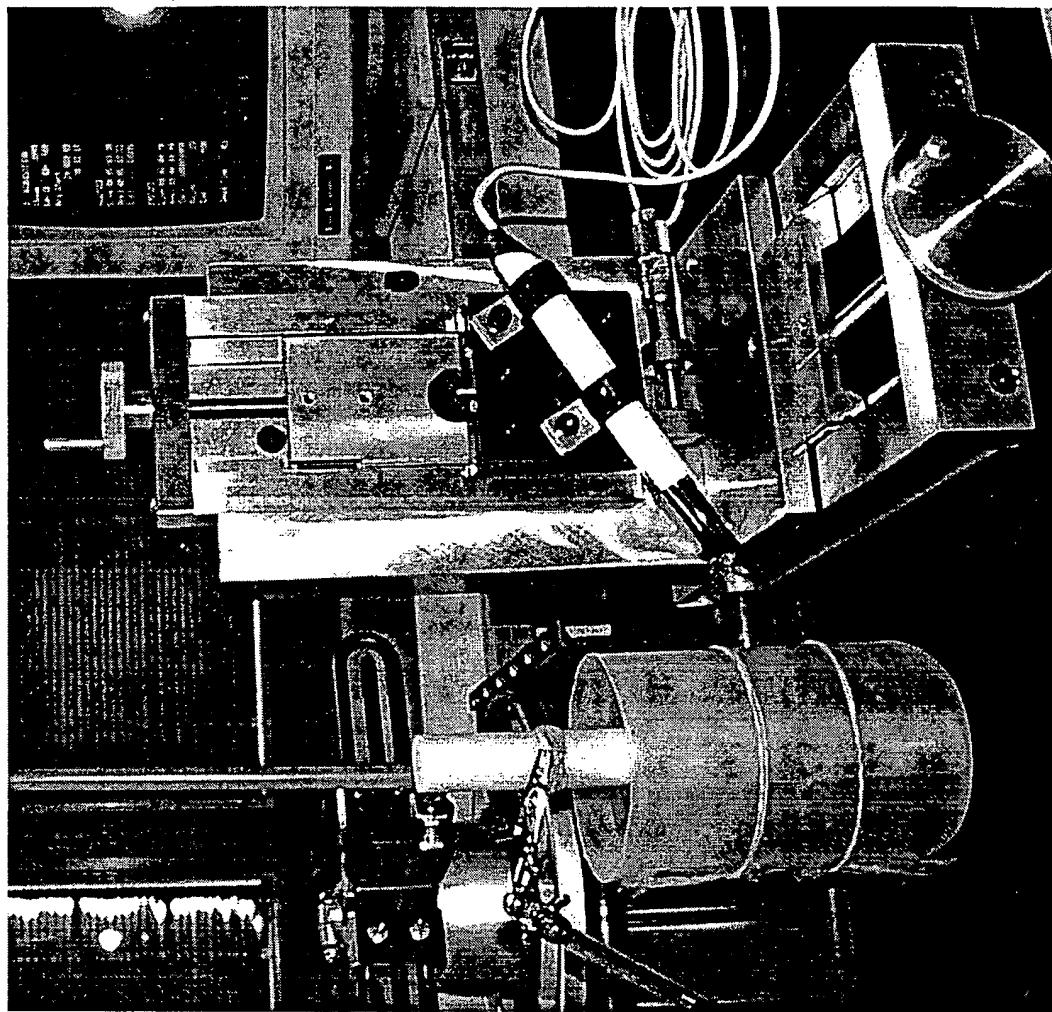
# Experimental Setup



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## Experimental Setup (cont.)

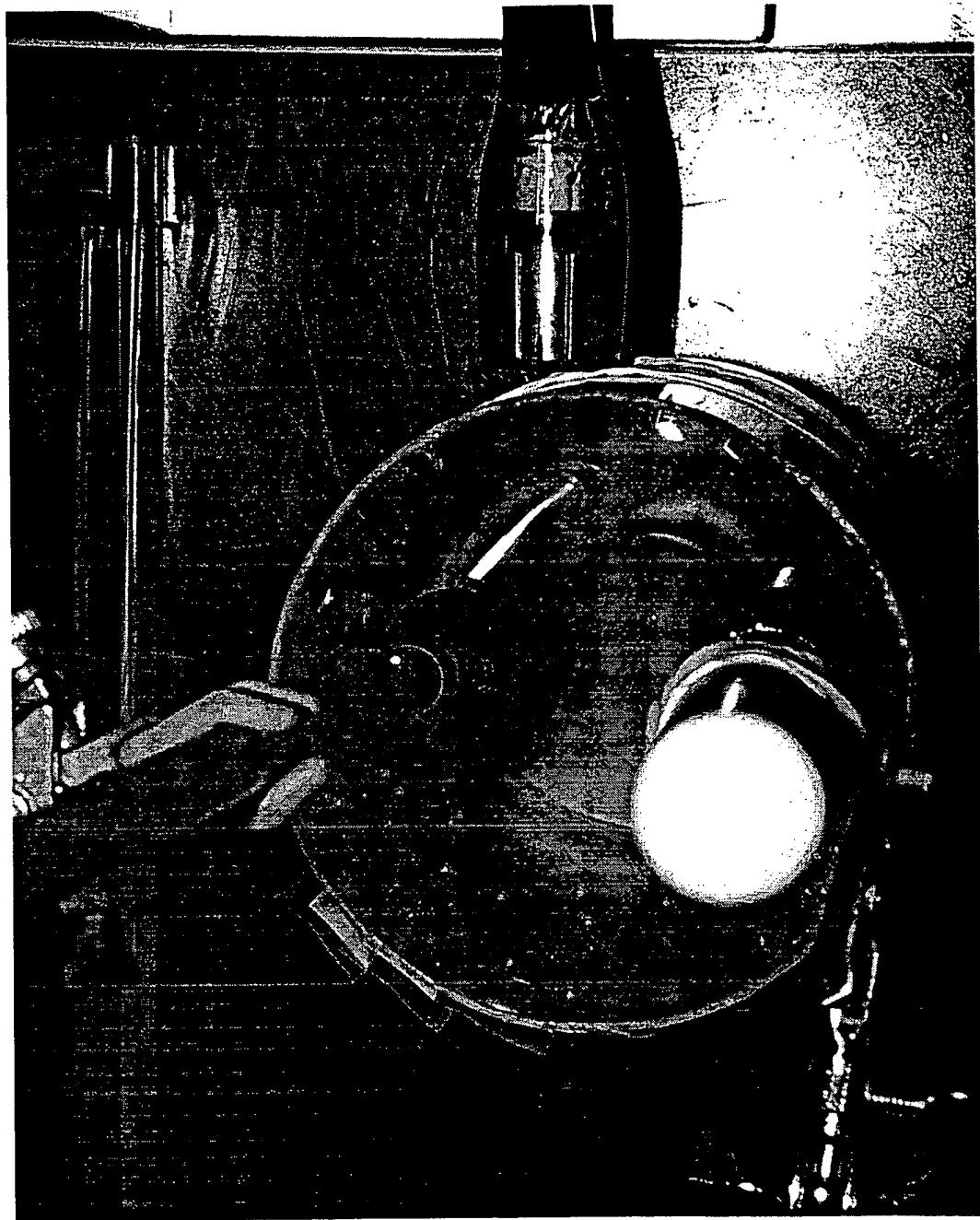


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# Experimental Setup (cont.)



Medrad Extravasation Phase 2, 6-8-99



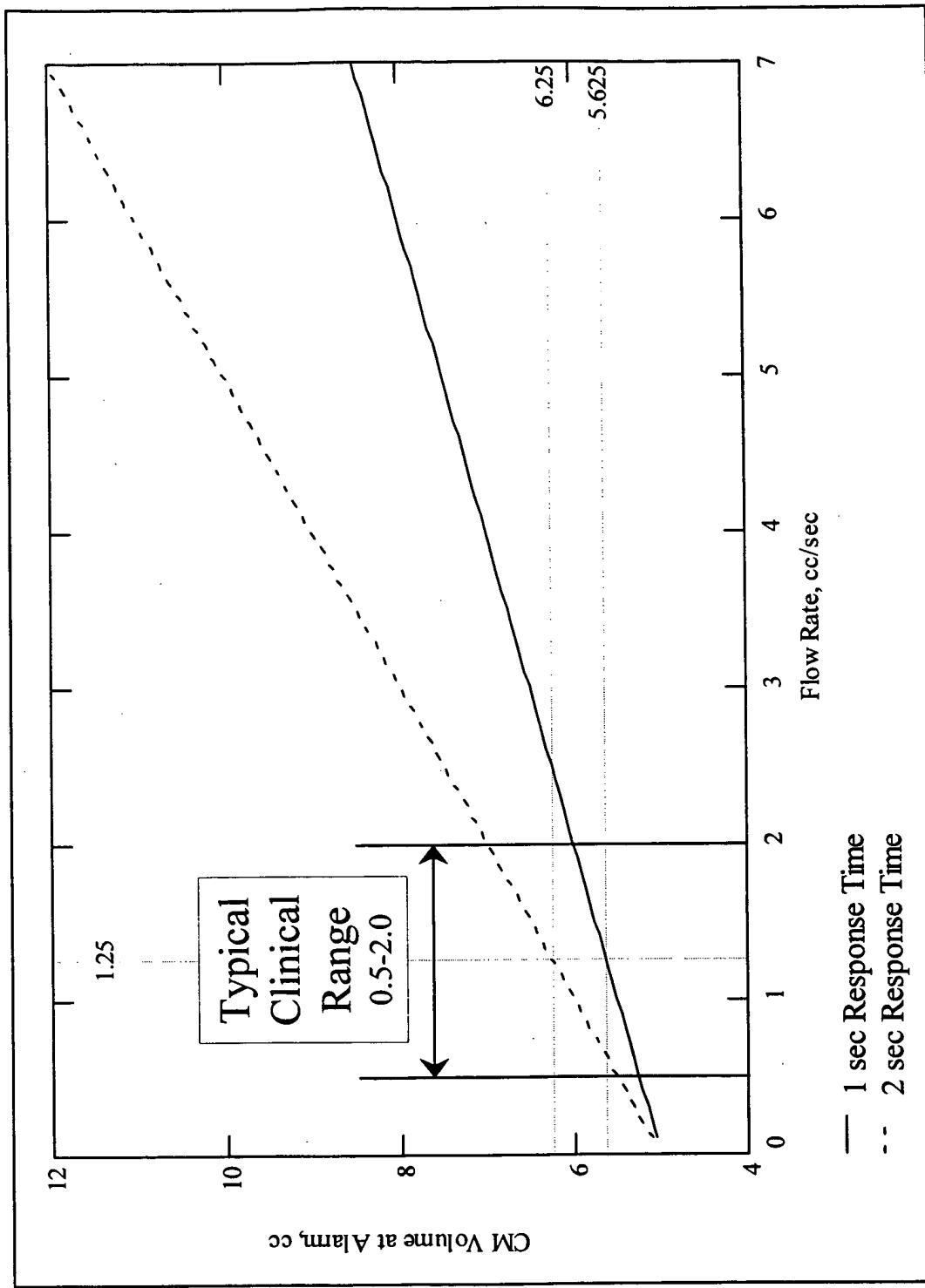
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# Performance Goals and Criteria

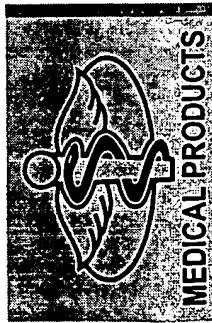
- Detect  $\leq 5$ cc of CM (370 mgI/mL)
- Response time of 2 sec or less
- At what volume of CM does the system alarm? (Function of *leak* flow rate)



# Performance Goals and Criteria (cont.)



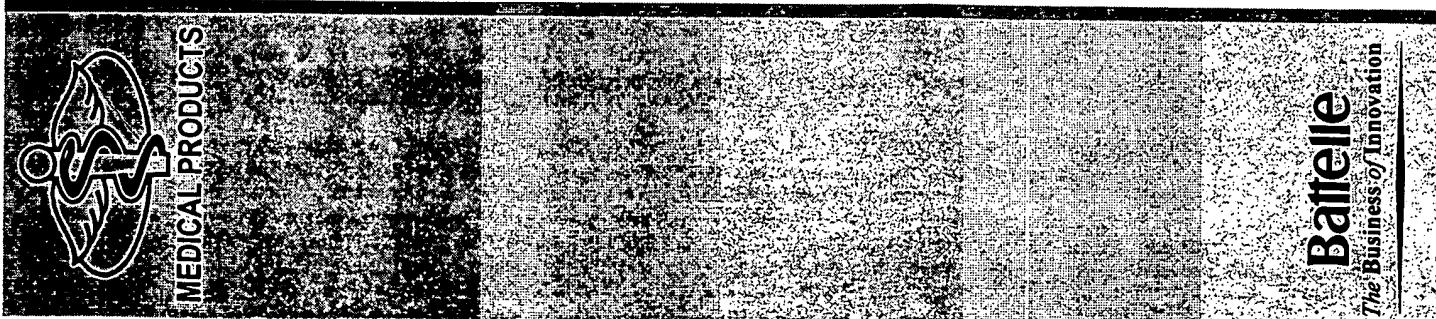
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# Performance Goals and Criteria (cont.)

- Dose to patient is small fraction of CT dose
- False positive (alarm) probability of 1%
  - System alarms in about 1 out of 100 procedures (20 min)
  - Competition is at 3% false alarm probability
- False negative probability of 1%
  - No alarm occurs when it *should*
  - Low false negative prob. improves response time validity



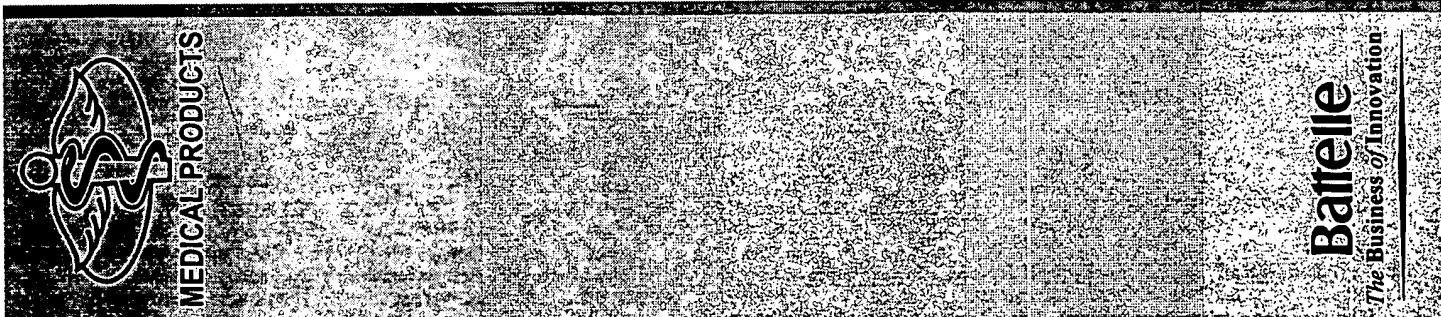
## Experiment and Analysis Steps

- Acquire accurate Baseline Counts (balloon deflated) for 3 detector and 4 target locations
- Acquire accurate Target Counts (5cc of CM added to balloon via syringe) for 3 detector and 4 target locations
- Determine Percentage Count Reduction (PCR) for 16 configurations ([3 individual detectors + 1 sum] x [4 target locations])



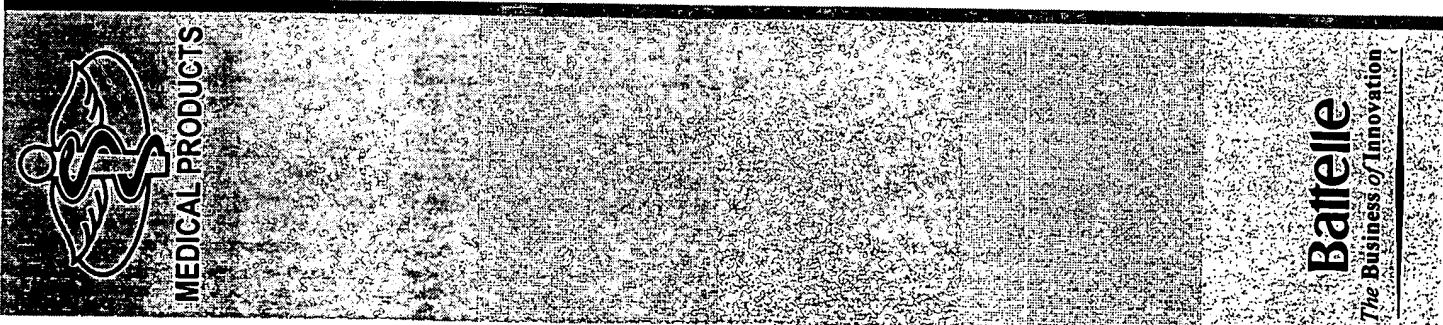
## Experiment and Analysis Steps (cont.)

- Calculate required PCR margin = 7%  
(S-D motion margin + Baseline & Target Count accuracy - i.e. confidence interval)
- Determine which target-detector configurations satisfied PCR margin
- Measure source dose rate and predict patient dose from source array
- Complete S-D motion experiment
- With and without simulated bone



## Experiment and Analysis Results

- Satisfied detection margin (7%) for 13 of the 16 target-detector configurations (two of the detector configurations worked for all 4 target locations)



# Experiment and Analysis Results (cont.)

Percentage Count Reduction (PCR), %				
Target Location	D1	D2	D3	D1+D2+D3
T1	38, 43 <sup>3</sup>	21, 22 <sup>3</sup>	9, 10 <sup>3</sup>	23, 25 <sup>3</sup>
T2	14, 17 <sup>3</sup>	8, 7 <sup>1,3</sup>	6 <sup>1</sup> , 9 <sup>3</sup>	9, 12 <sup>3</sup>
T3	7 <sup>1</sup>	16	25.8, 26.3 <sup>2</sup>	15
T4	4 <sup>1</sup>	9	12	8

<sup>1</sup> Less than or equal to total margin for measurement error (2-4%) and source-detector motion (3% for 2mm case).

<sup>2</sup> Simulated bone excluded from phantom.

<sup>3</sup> Narrow energy window used around photopeak to increase PCR.

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## Experiment and Analysis Results (cont.)

- Extensive statistical analysis showed system can achieve stipulated response time and false positive/negative probabilities (see *Phantom Data and Primary Analysis*)
- Dose measurements and data analysis shows if CZT (highly efficient detector) is used the required dose to patient is...



# Performance Results (cont.)

Calculated Dose for 20 Minute Exposure, Units: % of Brain CT Dose

Target Location	D1	D2	D3	D1+D2+D3
T1	0.24, 0.32 <sup>3</sup>	0.28, 0.38 <sup>3</sup>	0.32, 0.42 <sup>3</sup>	0.22, 0.26 <sup>3</sup>
T2	0.30, 0.38 <sup>3</sup>	0.32, 0.42 <sup>3</sup>	0.32 <sup>1</sup> , 0.42 <sup>3</sup>	0.26, 0.30 <sup>3</sup>
T3	0.32	0.30	0.29, 0.28 <sup>2</sup>	0.24
T4	0.32	0.32	0.32	0.26

<sup>1</sup> May be higher if new source-detector configuration is used to increase PCR.

<sup>2</sup> Simulated bone excluded from phantom.

<sup>3</sup> Narrow energy window used around photopeak to increase PCR.

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# Performance Results (cont.)

## Dose references for comparison:

Brain CT Exam dose: 200-400 mrem

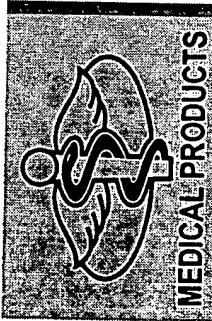
Abdominal CT: 2000 mrem

Dental X-ray: 10 mrem

Medrad Device  
(Calculated 20 min exp.): 0.64 mrem

**Note:** For a 9.5% efficient detector, multiply above doses by 10

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# Performance Impact Chart

Note: From outside sources

CM Content in Veins  
(if baseline count taken before injection)

Minimum PCR Required

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Patient Anatomy

Source-Detector Configuration

Extravasation Detectable?

Baseline Count Accuracy

Baseline Count Time Length

Patient Arm / Device Motion

CT Scatter Level

Achievable Response Time & False Pos./Neg. Probabilities

Source Activity & Position

Detector Efficiency

PCR

Extravasation Location, Size, and Shape

CM Concentration

Patient Dose

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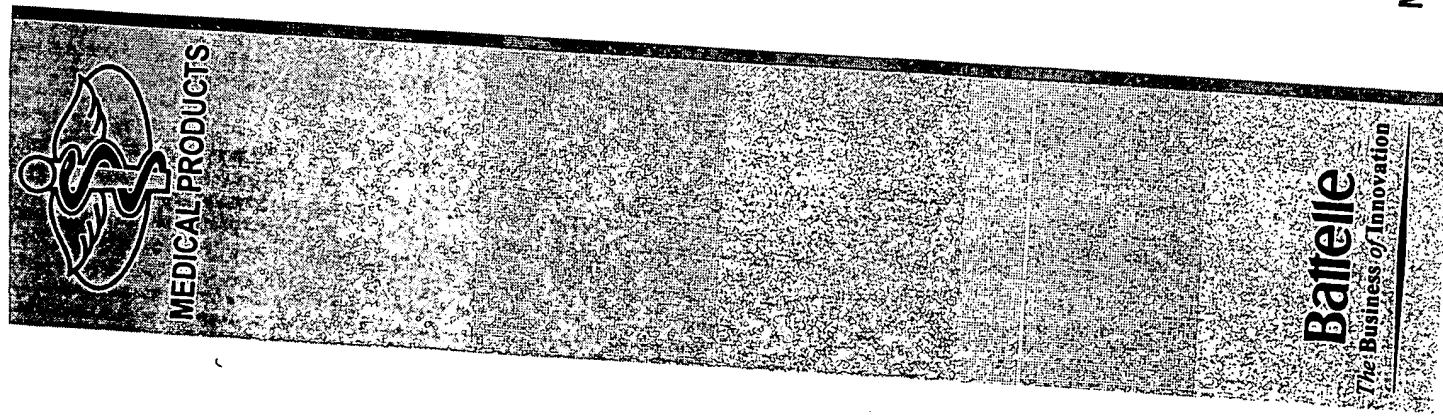
## Key Conclusions (Combining Phases 1 & 2)

- Larger detector surface area (D1+D2+D3):
  - Often decreased PCR ("shadow") - increased PCR if more target in S-D direct path
  - Always decreased predicted patient dose
- Single detector (D2) in conjunction with source array detected all targets (T1-T4) within PCR margin
- PCR may need to be improved in certain sub-regions



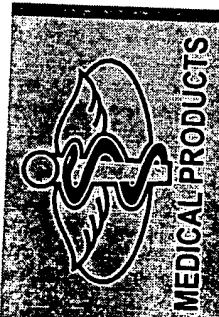
## Key Conclusions (Combining Phases 1 & 2)

- PCR will decrease several percentage points when lower concentration CM is used
- May be able to increase PCR significantly by using lower energy photons (I-129) with small increase to patient dose



## Current Questions

- When should the baseline count be made relative to CM injection?
- Before injection? If so, what is the total volume and blood concentration of CM in veins located in the search region? (If large this increases PCR margin)
- What other target locations should be considered?  
Under/behind bone?



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# Suggested Future Phase Work

- Address current questions
- Develop computer model/simulation to increase PCR in certain parts of the search region
  - Optimize source array layout and detector(s) position
  - Optimize photon energy used
- Further investigate detector technologies
- Consider non-intrusive approaches to placing sources and detectors near search region while allowing palpitation (cradle, strap, etc.)



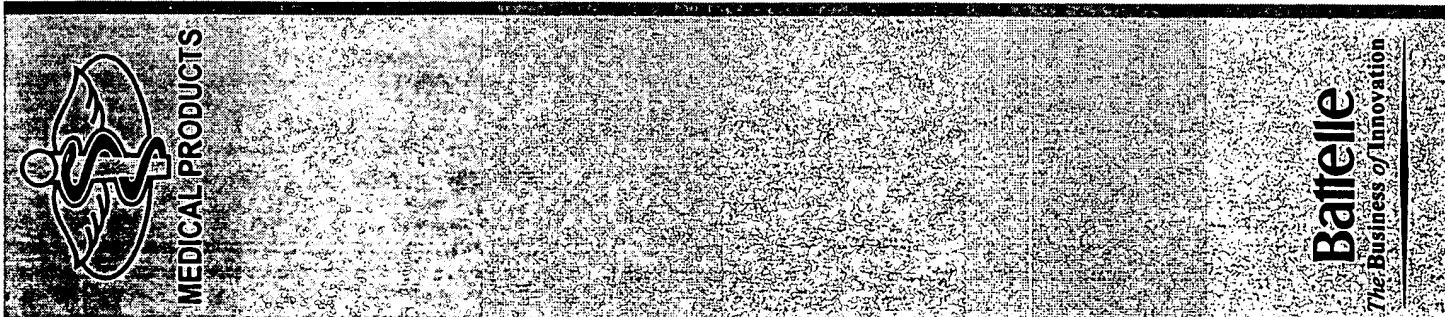
## Suggested Future Phase Work (cont.)

- Develop a physical model with optimized source-detector array configuration and non-optimized signal processing algorithms for functional experiments with human phantom
- Further investigate the following by using computer model:
  - Patient-device relative motion
  - Patient limb motion (flexing, bending, etc.)
  - Source-detector relative motion
- Obtain accurate CT scatter data or measurements for old and new generation CT scanners



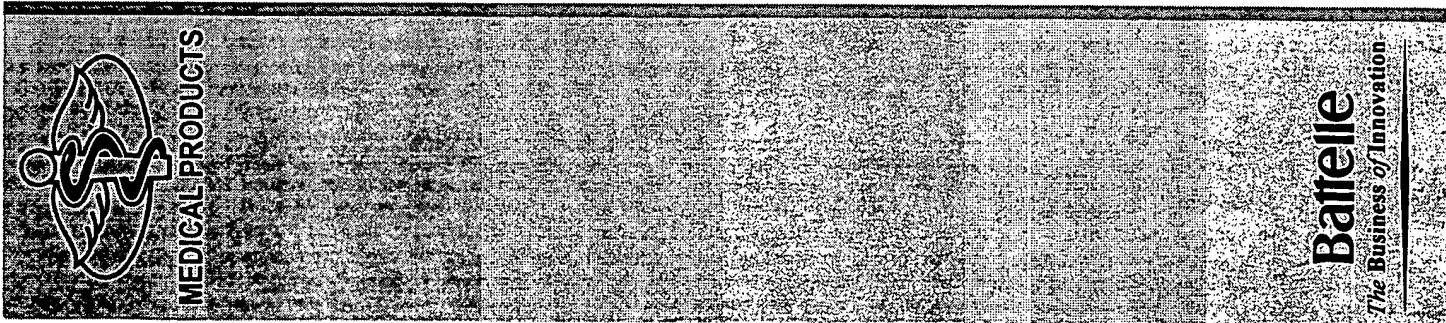
# Selected Phase Work Details

Medrad Extravasation Phase 2 (6-8-99)

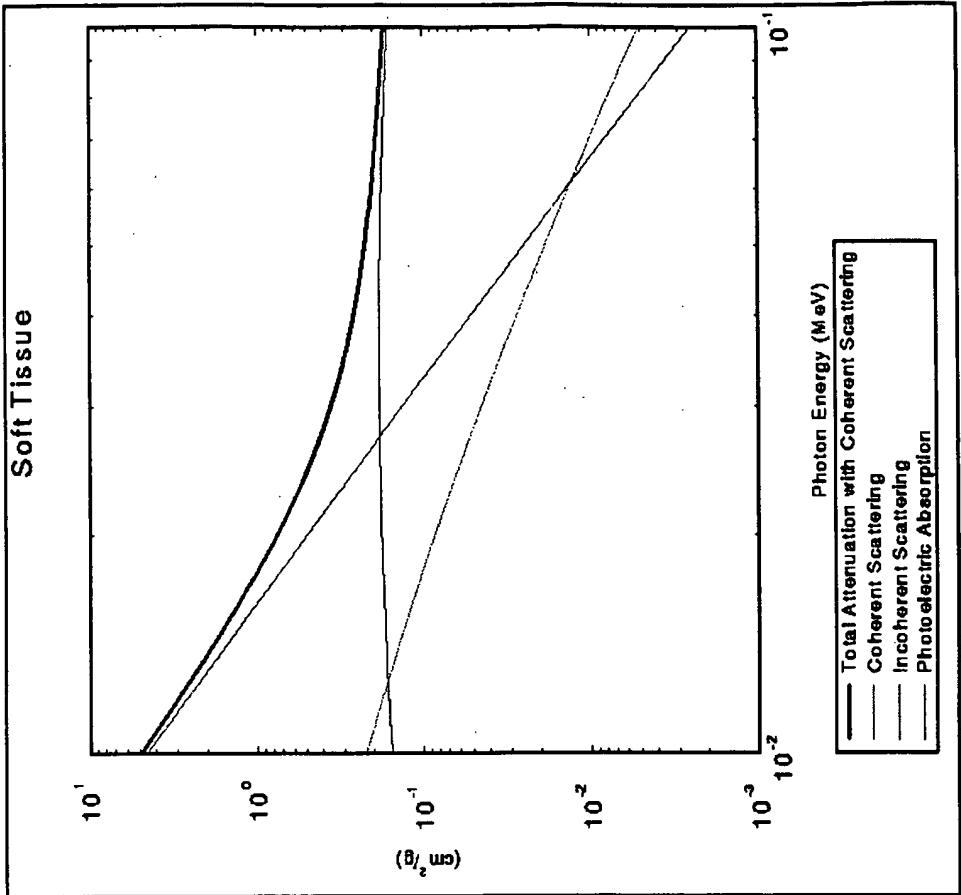
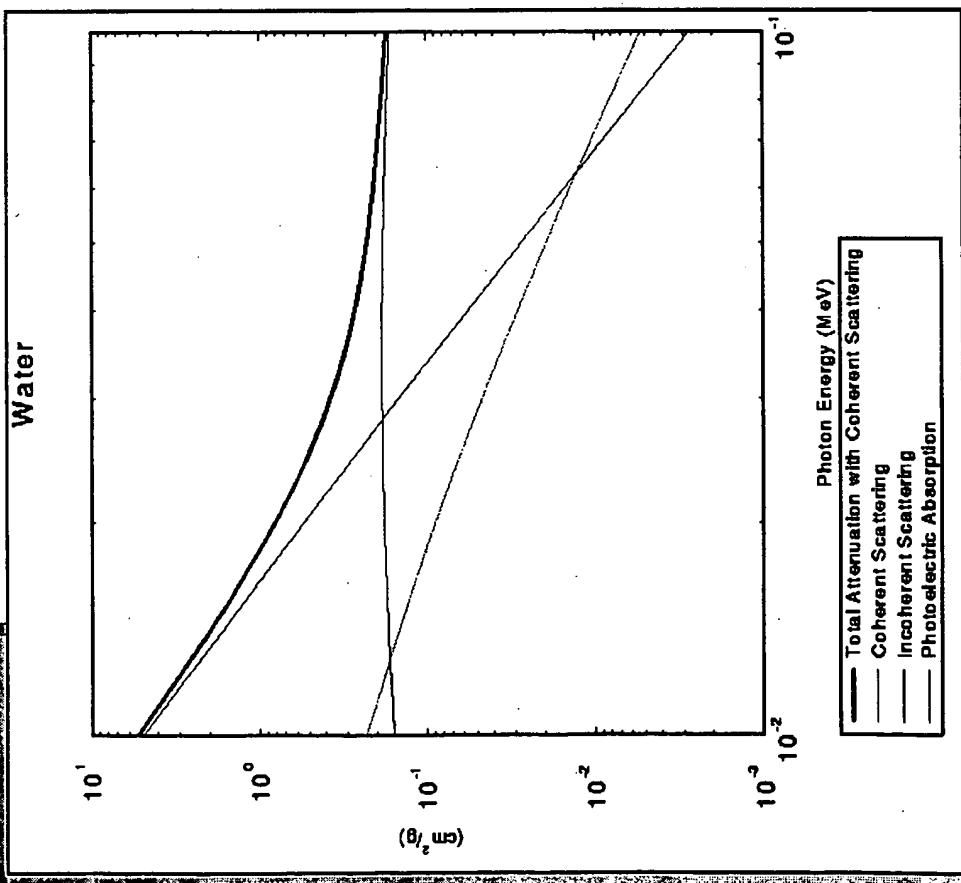
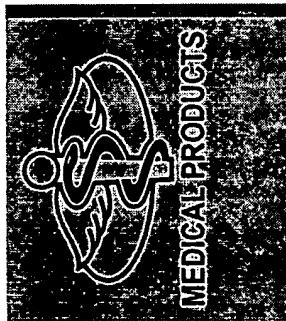


# Alternative Detector Technologies

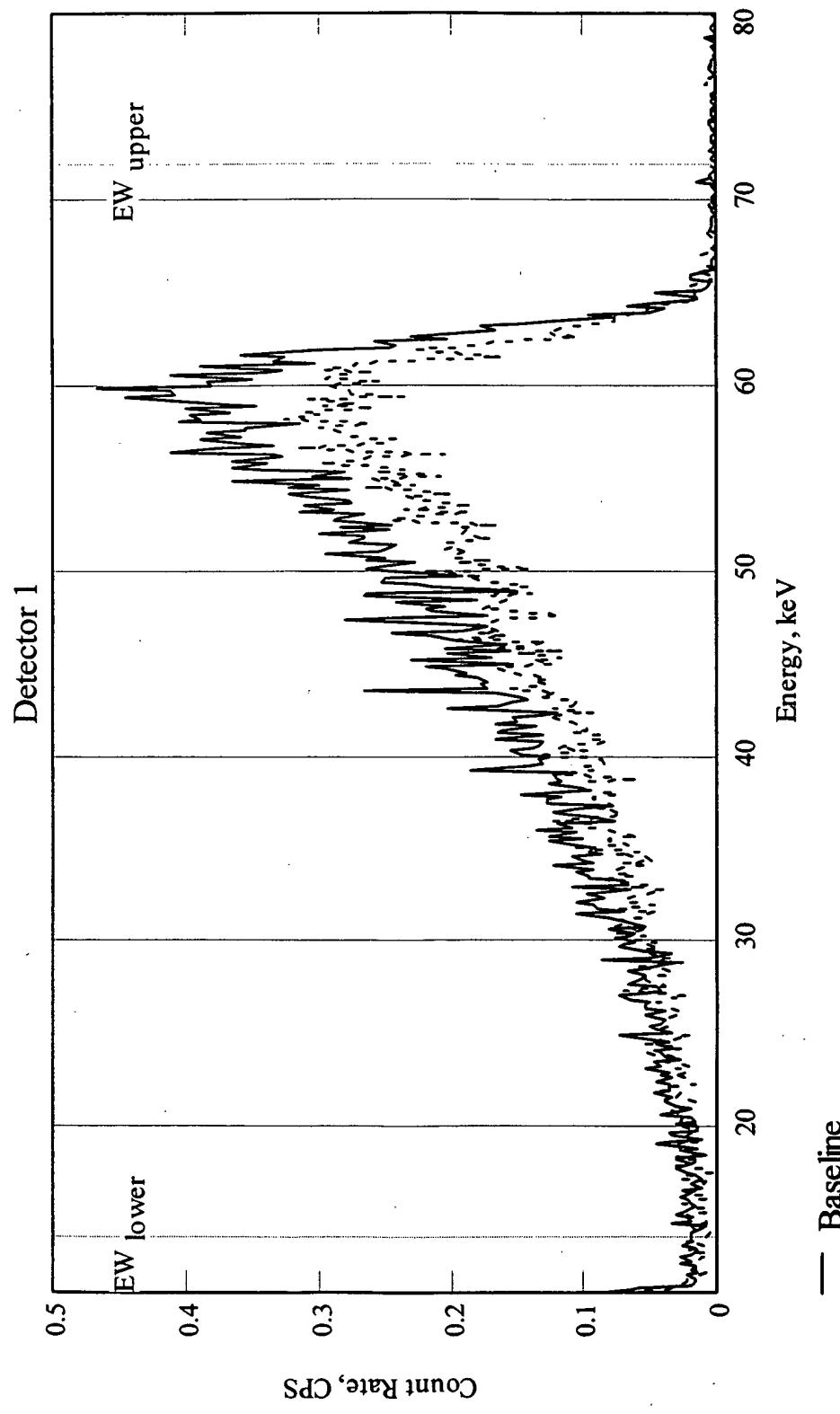
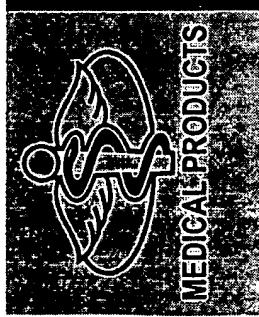
- Xenon (Xe) - filled tube
  - Proportional counter
  - More efficient than GM (Neon-Halogen)
  - Higher voltage: Xe=1650VDC (GM=900VDC)
- Silicon (Si) diodes
  - Only slightly more efficient than GM
  - Inexpensive in quantity (see Appendix for details)
- Amorphous Selenium (aSe)
  - High efficiency (possibly > 60%)
  - Gaining popularity for digital x-rays (possibly affordable)
- Scintillating fiber: Battelle-managed Pacific Northwest National Laboratory (PNNL) - Needs more examination



# Simulating Soft Tissue



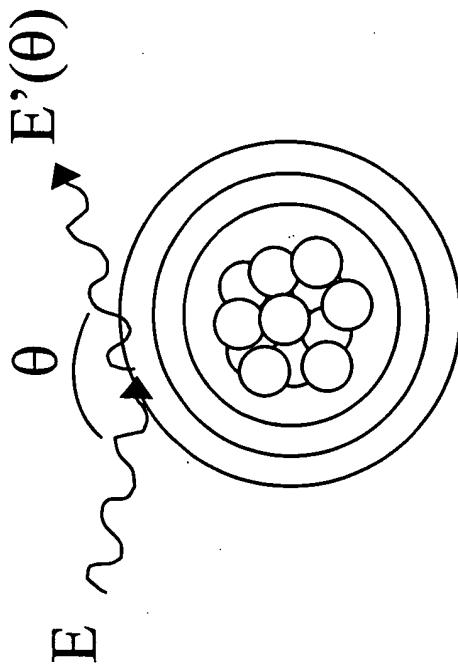
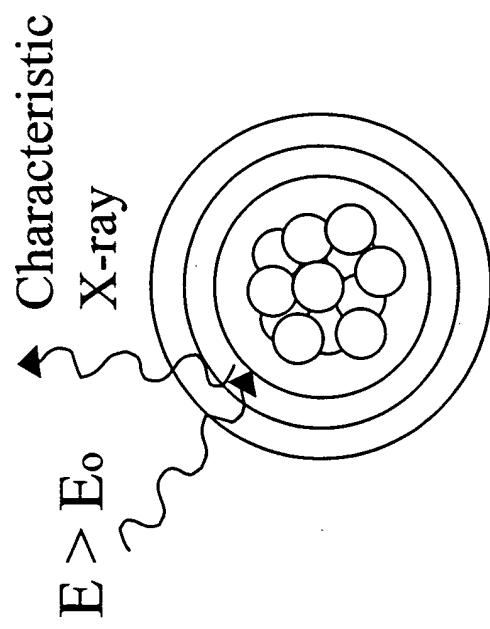
# Using Energy Spectral Analysis



# New Concepts for Modes of Detection

- **X-ray fluorescence**

In studying iodine scattering and absorption properties, observed fluorescence at 33.17 keV -  
Idea: bombard with  $E > E_o$  and use energy windowing to detect 33.17 keV and below



- **Scatter mode**

Back = co-located S-D



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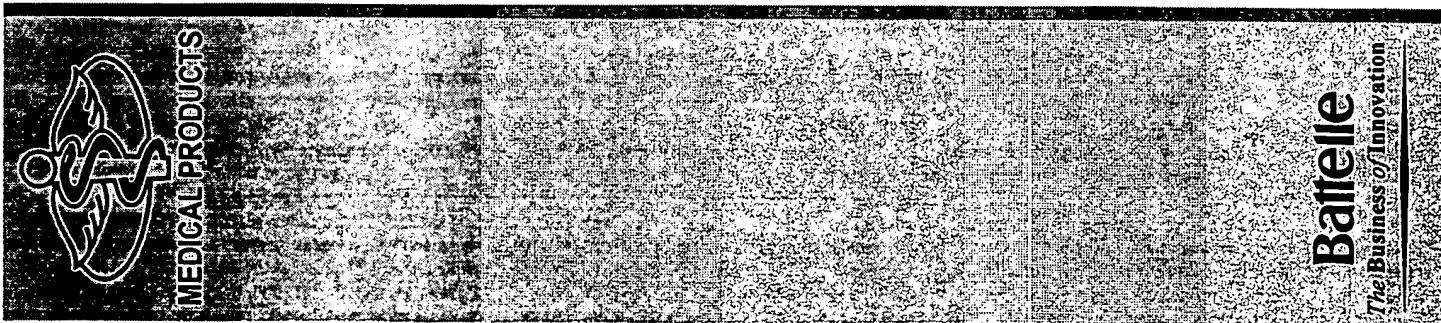
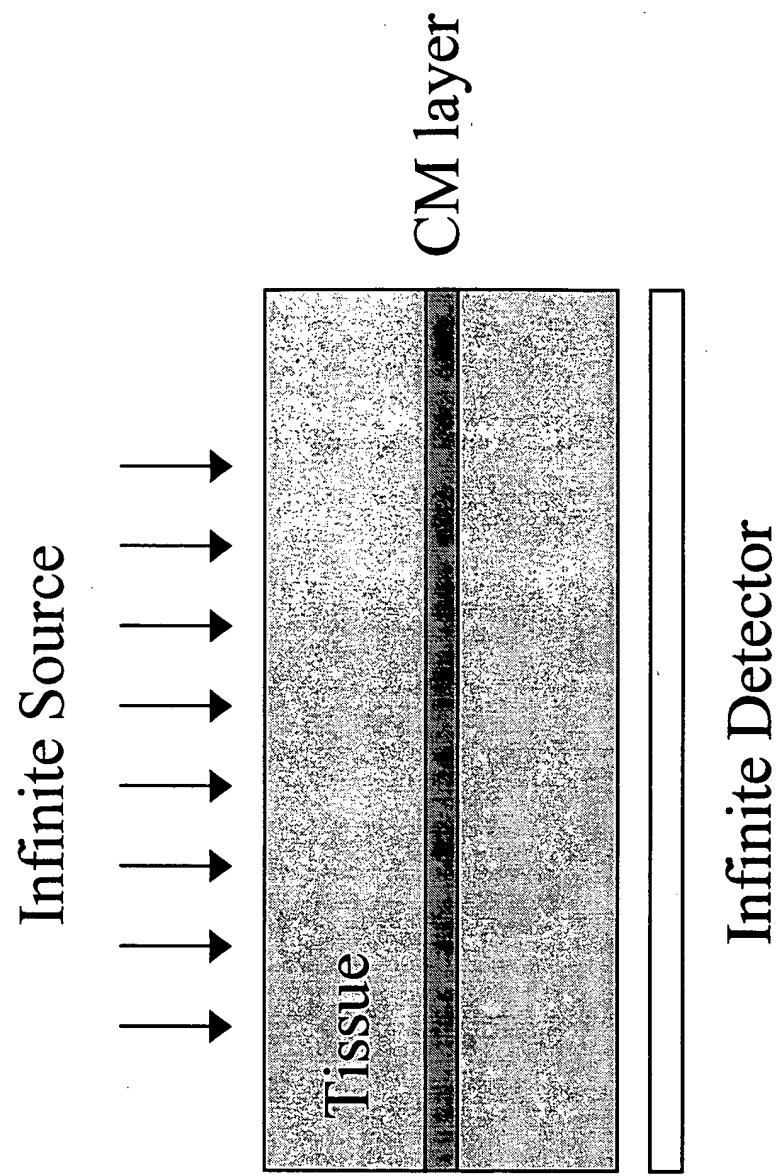
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## Superior Source: Iodine-129

- “Iodine” just coincidence
- Large jump in absorption just after fluorescence energy 33.17 keV was observed
- Created a simple model



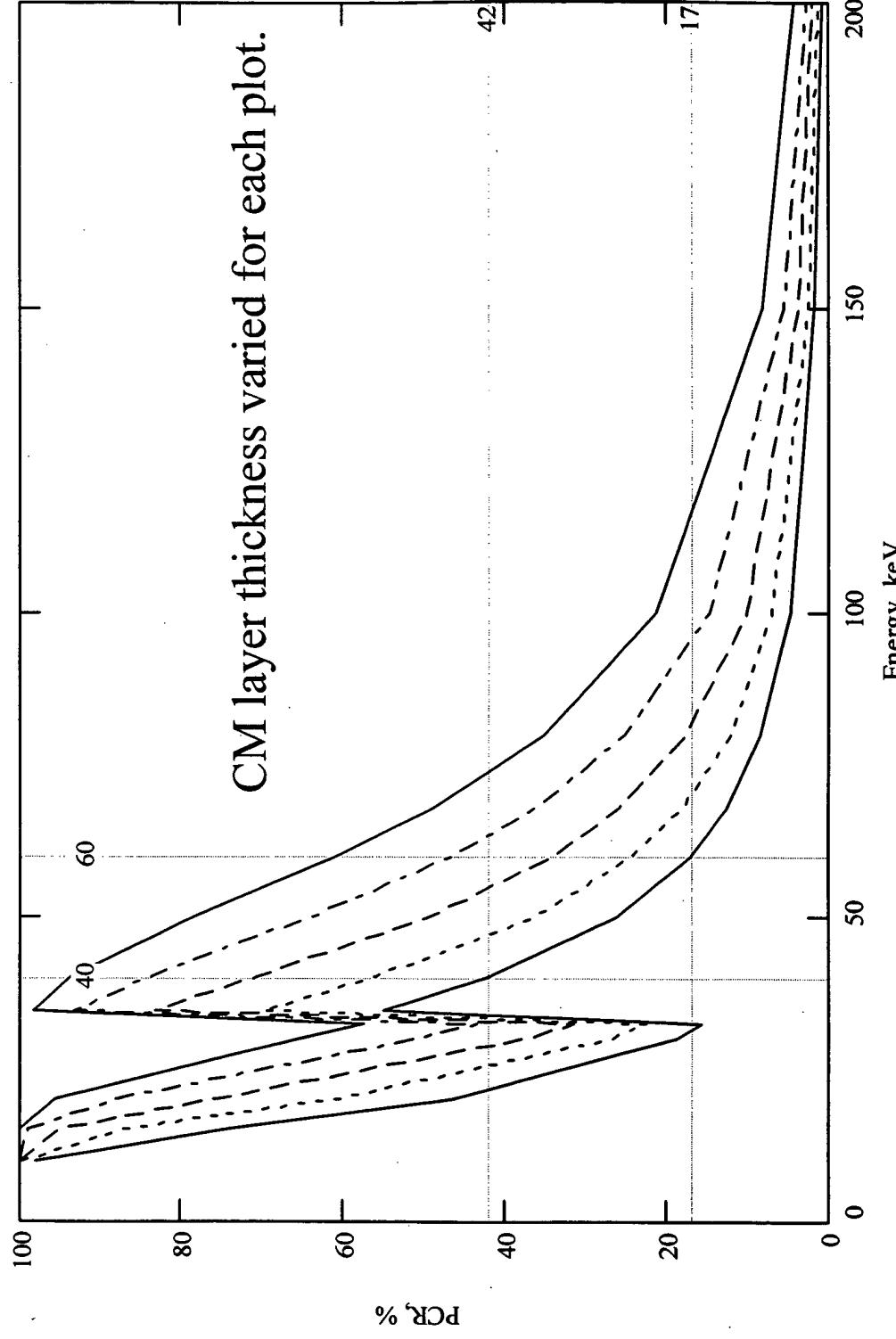
## Superior Source: Iodine-129 (cont.)



## Superior Source: Iodine-129 (cont.)

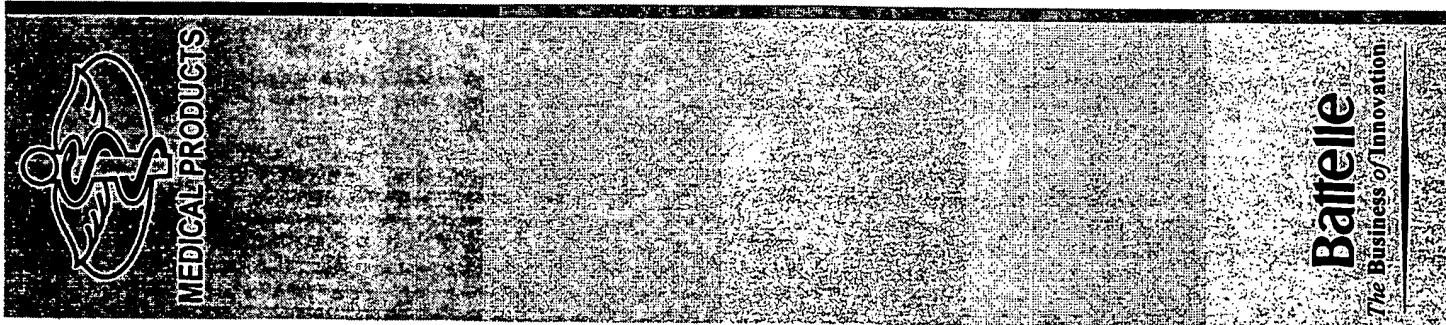


MEDICAL PRODUCTS

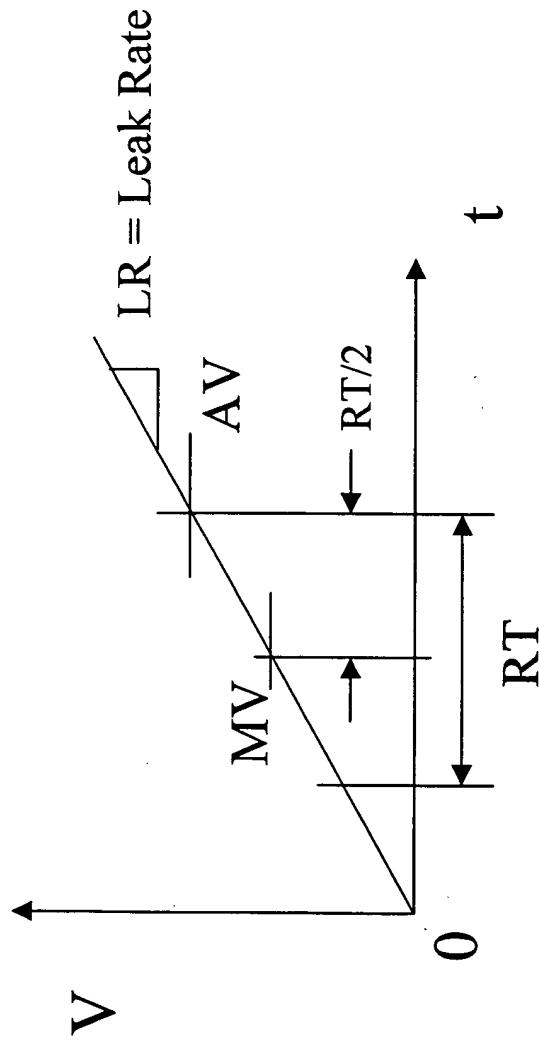


## Superior Source: Iodine-129 (cont.)

- Searched for nuclides emitting EM rays with energies  $> 33.17$  keV and with long half-lives
- Found I-129: Photopeak = 40 keV
- May be possible to make I-129 array or planar type within desired source UMC



## Effect of CM Leak Rate



RT = Response Time. (Algorithm lag time.)  
MV = Mean Volume (Target Volume) that system and algorithm responds to.  
AV = Alarm Volume. Volume reached when alarm should (with high probability) start.

$AV = MV + LR * (RT/2)$ . If  $MV = 5cc$ ,  $LR = 2cc/sec$ , and  $RT = 2sec$ , then  $AV = 7cc$ . If we choose  $MV = 5cc$ ,  $LR = 0.75cc/sec$ , and  $RT = 2 sec$ , then  $AV = 5.75cc$ . Let me know what you'd like.

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